METHYLPREDNISOLONE SODIUM SUCCINATE - methylprednisolone sodium succinate injection, powder, lyophilized, for solution

Bedford Laboratories

Rx ONLY

For Intravenous or Intramuscular Administration

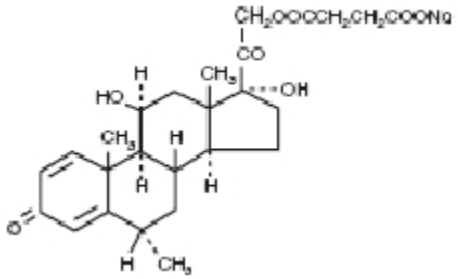
DESCRIPTION

Methylprednisolone Sodium Succinate for Injection USP sterile powder contains methylprednisolone sodium succinate as the active ingredient.

Methylprednisolone sodium succinate occurs as a white, or nearly white, odorless hygroscopic, amorphous solid. It is very soluble in water and in alcohol; it is insoluble in chloroform and is very slightly soluble in acetone.

The chemical name for methylprednisolone sodium succinate is 11β,17,21-Trihydroxy-6α-methylpregna-1,4-diene-3,20-dione 21-(sodium succinate), and the molecular weight is 496.53.

The structural formula is represented below:



Methylprednisolone sodium succinate is so extremely soluble in water that it may be administered in a small volume of diluent and is especially well suited for intravenous use in situations in which high blood levels of methylprednisoIone are required rapidly.

Methylprednisolone sodium succinate for injection is available in several strengths and packages for intravenous or intramuscular administration.

500 mg Multi-Dose Vial - Each 8 mL (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 500 mg methylprednisolone; also 6.4 mg monobasic sodium phosphate anhydrous; 69.6 mg dibasic sodium phosphate dried.

1 gram Multi-Dose Vial - Each 16 mL (when mixed as directed) contains methylprednisolone sodium succinate equivalent to 1 gram methylprednisolone; also 12.8 mg monobasic sodium phosphate anhydrous; 139.2 mg dibasic sodium phosphate dried.

When necessary, the pH of each formula was adjusted with sodium hydroxide so that the pH of the reconstituted solution is within the USP specified range of 7 to 8 and the tonicities are for the 500 mg per 8 mL and 1 gram per 16 mL solutions, 0.40 osmolar. (Isotonic saline = 0.28 osmolar).

IMPORTANT – Use only Bacteriostatic Water For Injection with Benzyl Alcohol when reconstituting Methylprednisolone Sodium Succinate for Injection USP.

Use within 48 hours after mixing.

CLINICAL PHARMACOLOGY

Methylprednisolone is a potent anti-inflammatory steroid with greater anti-inflammatory potency than prednisolone and even less tendency than prednisolone to induce sodium and water retention.

Methylprednisolone sodium succinate has the same metabolic and anti-inflammatory actions as methylprednisolone. When given parenterally and in equimolar quantities, the two compounds are equivalent in biologic activity. The relative potency of methylprednisolone and hydrocortisone sodium succinate, as indicated by depression of eosinophil count, following intravenous administration, is at least four to one. This is in good agreement with the relative oral potency of methylprednisolone and hydrocortisone.

INDICATIONS AND USAGE

When oral therapy is not feasible, and the strength, dosage form and route of administration of the drug reasonably lend the preparation to the treatment of the condition, methylprednisolone sodium succinate for injection is indicated for intravenous or intramuscular use in the following conditions:

1. Endocrine Disorders

• Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy, mineralocorticoid supplementation is of particular importance)

• Acute adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; mineralocorticoid supplementation may be necessary, particularly when synthetic analogs are used)

• Preoperatively and in the event of serious trauma or illness, in patients with known adrenal insufficiency or when adrenocortical reserve is doubtful

• Shock unresponsive to conventional therapy if adrenocortical insufficiency exists or is suspected
• Congenital adrenal hyperplasia
• Nonsuppurative thyroiditis
• Hypercalcemia associated with cancer

2. Rheumatic Disorders

As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in:
• Post-traumatic osteoarthritis
• Synovitis of osteoarthritis
• Rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy)
• Acute and subacute bursitis
• Epicondylitis
• Acute nonspecific tenosynovitis
• Acute gouty arthritis
• Psoriatic arthritis
• Ankylosing spondylitis

3. Collagen Diseases

During an exacerbation or as maintenance therapy in selected cases of:
• Systemic lupus erythematosus
• Acute rheumatic carditis
• Systemic dermatomyositis (polymyositis)

4. Dermatologic Diseases

• Pemphigus
• Severe erythema multiforme (Stevens-Johnson syndrome)
• Exfoliative dermatitis
• Bullous dermatitis herpetiformis
• Severe seborrheic dermatitis
• Severe psoriasis
• Mycosis fungoides

5. Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in:
• Bronchial asthma
• Contact dermatitis
• Atopic dermatitis
• Serum sickness
• Seasonal or perennial allergic rhinitis
• Drug hypersensitivity reactions
• Urticarial transfusion reactions
• Acute noninfectious laryngeal edema (epinephrine is the drug of first choice)

6. Ophthalmic Diseases

Severe acute and chronic allergic and inflammatory processes involving the eye, such as:
• Herpes zoster ophthalmicus
• Iritis, iridocyclitis
• Chorioretinitis
• Diffuse posterior uveitis and choroiditis
• Optic neuritis
• Sympathetic ophthalmia
• Anterior segment inflammation
• Allergic conjunctivitis
• Allergic corneal marginal ulcers
• Keratitis

7. Gastrointestinal Diseases

To tide the patient over a critical period of the disease in:
• Ulcerative colitis (systemic therapy)
• Regional enteritis (systemic therapy)

8. Respiratory Diseases

• Symptomatic sarcoidosis
• Berylliosis
• Fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy
• Loeffler's syndrome not manageable by other means
• Aspiration pneumonitis

9. Hematologic Disorders
• Acquired (autoimmune) hemolytic anemia
• Idiopathic thrombocytopenic purpura in adults (IV only; IM administration is contraindicated)
• Secondary thrombocytopenia in adults
• Erythroblastopenia (RBC anemia)
• Congenital (erythroid) hypoplastic anemia
10. Neoplastic Diseases
For palliative management of:
• Leukemias and lymphomas in adults
• Acute leukemia of childhood
11. Edematous States
• To induce diuresis or remission of proteinuria in the nephrotic syndrome, without uremia, of the idiopathic type or that due to lupus erythematosus
12. Nervous System
• Acute exacerbations of multiple sclerosis
13. Miscellaneous
• Tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy
• Trichinosis with neurologic or myocardial involvement

CONTRAINDICATIONS
The use of methylprednisolone sodium succinate for injection is contraindicated in premature infants because the recommended diluent contains benzyl alcohol. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants. Methylprednisolone sodium succinate for injection is also contraindicated in systemic fungal infections and patients with known hypersensitivity to the product and its constituents.

WARNINGS
In patients on corticosteroid therapy subjected to any unusual stress, increased dosage of rapidly acting corticosteroids before, during, and after the stressful situation is indicated.
Corticosteroids may mask some signs of infection, and new infections may appear during their use. There may be decreased resistance and inability to localize infection when corticosteroids are used.
A study has failed to establish the efficacy of methylprednisolone in the treatment of sepsis syndrome and septic shock. The study also suggests that treatment of these conditions with methylprednisolone may increase the risk of mortality in certain patients (i.e., patients with elevated serum creatinine levels or patients who develop secondary infections after methylprednisolone).
Prolonged use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to fungi or viruses.
Usage in pregnancy. Since adequate human reproduction studies have not been done with corticosteroids, the use of these drugs in pregnancy, nursing mothers, or women of childbearing potential requires that the possible benefits of the drug be weighed against the potential hazards to the mother and embryo or fetus. Infants born of mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.
Average and large doses of cortisone or hydrocortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.
While on corticosteroid therapy patients should not be vaccinated against smallpox. Other immunization procedures should not be undertaken in patients who are on corticosteroids, especially on high dose, because of possible hazards of neurological complications and a lack of antibody response.
The use of methylprednisolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with appropriate antituberculous regimen.
If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.
Because rare instances of anaphylactic (e.g., bronchospasm) reactions have occurred in patients receiving parenteral corticosteroid therapy, appropriate precautionary measures should be taken prior to administration, especially when the patient has a history of allergy to any drug.
There are reports of cardiac arrhythmias and/or circulatory collapse and/or cardiac arrest following the rapid administration of large IV doses of methylprednisolone (greater than 0.5 gram administered over a period of less than 10 minutes). Bradycardia has been reported during or after the administration of large doses of methylprednisolone sodium succinate, and may be unrelated to the speed or duration of infusion.
Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route

and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

PRECAUTIONS

General

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Corticosteroids should be used cautiously in patients with ocular herpes simplex because of possible corneal perforation.

The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer; renal insufficiency; hypertension; osteoporosis; and myasthenia gravis.

Growth and development of infants and children on prolonged corticosteroid therapy should be carefully observed.

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that corticosteroids affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **DOSAGE AND ADMINISTRATION**.)

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Interactions

Drug interactions

The pharmacokinetic interactions listed below are potentially clinically important. Mutual inhibition of metabolism occurs with concurrent use of cyclosporine and methylprednisolone; therefore, it is possible that adverse events associated with the individual use of either drug may be more apt to occur. Convulsions have been reported with concurrent use of methylprednisolone and cyclosporine.

Information for patients

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

ADVERSE REACTIONS

Fluid and Electrolyte Disturbances

- Sodium retention
- Fluid retention
- Congestive heart failure in susceptible patients
- Potassium loss
- Hypokalemic alkalosis
- Hypertension

Musculoskeletal

- Muscle weakness
- Steroid myopathy
- Loss of muscle mass
- Severe arthralgia
- Vertebral compression fractures
- Aseptic necrosis of femoral and humeral heads
- Pathologic fracture of long bones
- Osteoporosis

Gastrointestinal
• Peptic ulcer with possible perforation and hemorrhage
• Pancreatitis
• Abdominal distention
• Ulcerative esophagitis
Dermatologic
• Impaired wound healing
• Thin fragile skin
• Petechiae and ecchymoses
• Facial erythema
• Increased sweating
• May suppress reactions to skin tests
Neurological
• Increased intracranial pressure with papilledema (pseudo-tumor cerebri) usually after treatment
• Convulsions
• Vertigo
• Headache
Endocrine
• Development of Cushingoid state
• Suppression of growth in children
• Secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness
• Menstrual irregularities
• Decreased carbohydrate tolerance
• Manifestations of latent diabetes mellitus
• Increased requirements for insulin or oral hypoglycemic agents in diabetics
Ophthalmic
• Posterior subcapsular cataracts
• Increased intraocular pressure
• Glaucoma
• Exophthalmos
Metabolic
• Negative nitrogen balance due to protein catabolism
The following *additional* adverse reactions are related to parenteral corticosteroid therapy:
• Hyperpigmentation or hypopigmentation
• Subcutaneous and cutaneous atrophy
• Sterile abscess
• Anaphylactic reaction with or without circulatory collapse, cardiac arrest, bronchospasm
• Urticaria
• Nausea and vomiting
• Cardiac arrhythmias; hypotension or hypertension

DOSAGE AND ADMINISTRATION

When high dose therapy is desired, the recommended dose of methylprednisolone sodium succinate for injection is 30 mg/kg administered intravenously over at least 30 minutes. This dose may be repeated every 4 to 6 hours for 48 hours.
In general, high dose corticosteroid therapy should be continued only until the patient's condition has stabilized; usually not beyond 48 to 72 hours.
Although adverse effects associated with high dose short-term corticoid therapy are uncommon, peptic ulceration may occur. Prophylactic antacid therapy may be indicated.
In other indications initial dosage will vary from 10 to 40 mg of methylprednisolone sodium succinate for injection depending on the clinical problem being treated. The larger doses may be required for short-term management of severe, acute conditions. The initial dose usually should be given intravenously over a period of several minutes. Subsequent doses may be given intravenously or intramuscularly at intervals dictated by the patient's response and clinical condition. Corticoid therapy is an adjunct to, and not replacement for conventional therapy.
Dosage may be reduced for infants and children but should be governed more by the severity of the condition and response of the patient than by age or size. It should not be less than 0.5 mg per kg every 24 hours.
Dosage must be decreased or discontinued gradually when the drug has been administered for more than a few days. If a period of spontaneous remission occurs in a chronic condition, treatment should be discontinued. Routine laboratory studies, such as urinalysis, two-hour postprandial blood sugar, determination of blood pressure and body weight, and a chest X-ray should be made at regular intervals during prolonged therapy. Upper GI X-rays are desirable in patients with an ulcer history or significant dyspepsia.

Methylprednisolone sodium succinate for injection may be administered by intravenous or intramuscular injection or by intravenous infusion, the preferred method for initial emergency use being intravenous injection. To administer by intravenous (or intramuscular) injection, prepare solution as directed. The desired dose may be administered intravenously over a period of several minutes.
To prepare solutions for intravenous infusion, first prepare the solution for injection as directed. This solution may then be added to indicated amounts of 5% dextrose in water, isotonic saline solution or 5% dextrose in isotonic saline solution.

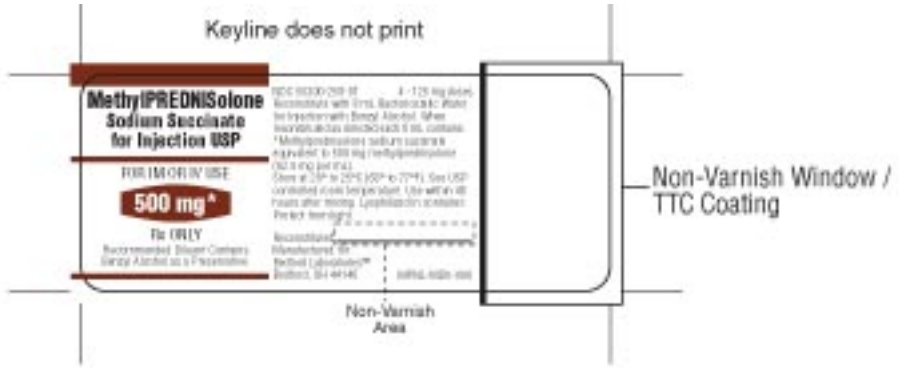
Multiple Sclerosis
In treatment of acute exacerbations of multiple sclerosis, daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day for 1 month have been shown to be effective (4 mg of methylprednisolone sodium succinate for injection is equivalent to 5 mg of prednisolone).

Storage Conditions
Protect from light.
Store unreconstituted product at 20° to 25°C (68° to 77°F). See USP controlled room temperature.
Store solution at 20° to 25°C (68° to 77°F). See USP controlled room temperature.
Use solution within 48 hours after mixing.

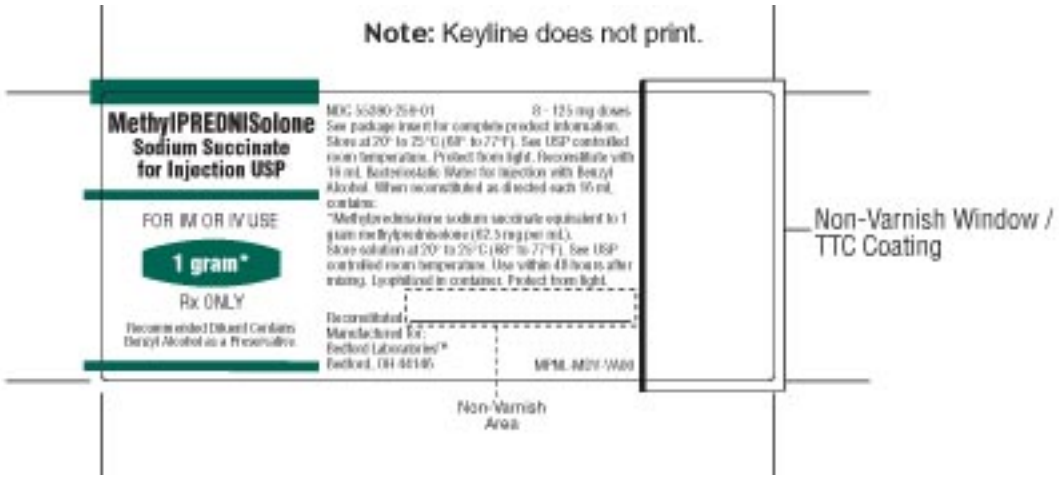
HOW SUPPLIED
Methylprednisolone Sodium Succinate for Injection USP is available in the following packages:
NDC 55390-258-01; 500 mg/vial (8 mL when mixed); Multi-Dose Vial; individually boxed.
NDC 55390-259-01; 1 g/vial (16 mL when mixed); Multi-Dose Vial; individually boxed.

Manufactured by:	Manufactured for:
Ben Venue Laboratories, Inc.	Bedford Laboratories™
Bedford, OH 44146	Bedford, OH 44146
August 2006	MPNL-MDV-P00

VIAL LABELS

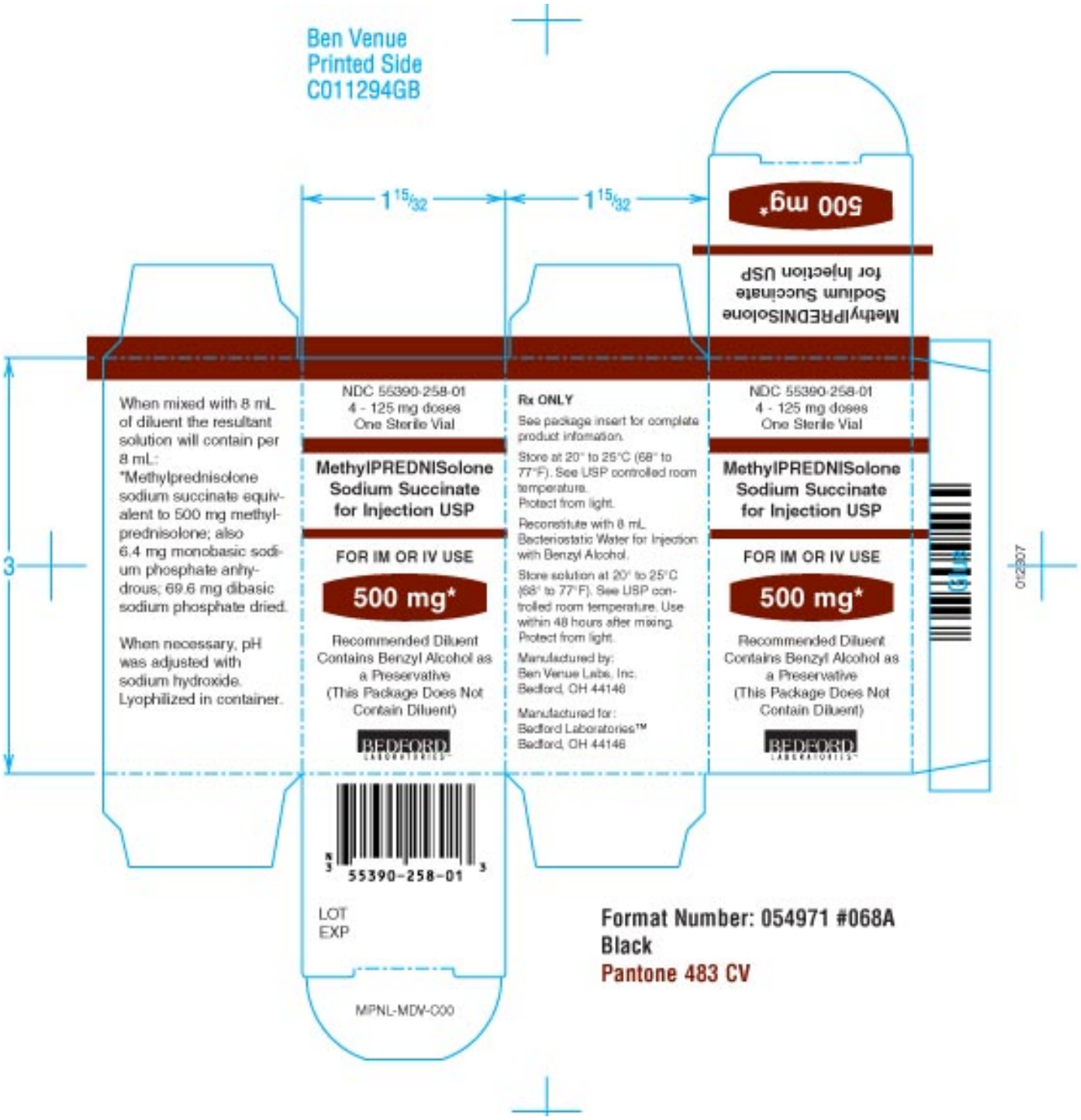


Vial Label 500 mg

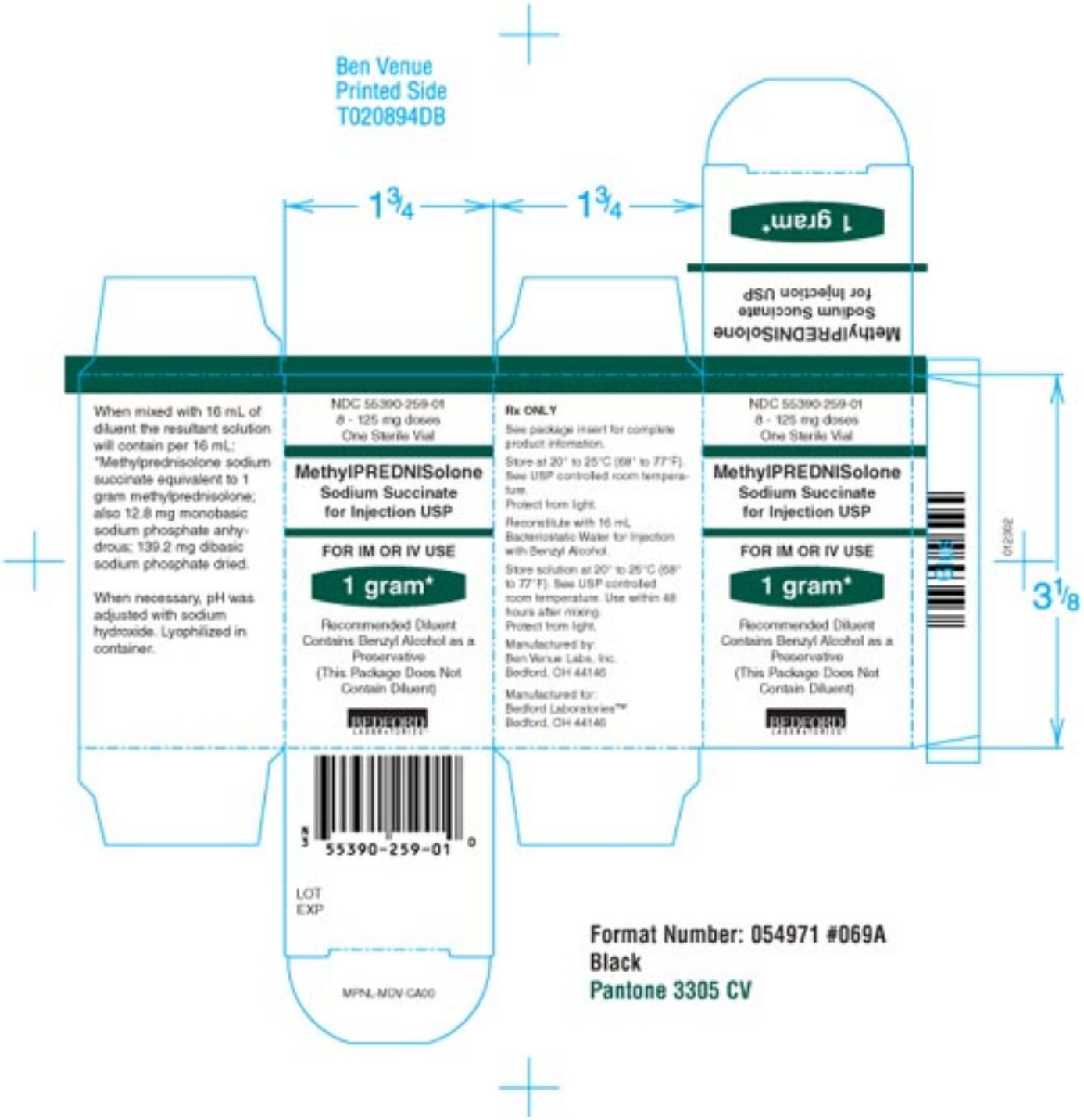


Vial Label 1 gram

CARTONS



Unit Carton 500 mg per vial



Unit Carton 1 gram per vial